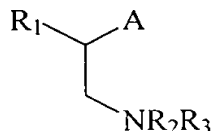


- 09022676-081604
1. A method for inhibiting epileptogenesis in a subject, comprising administering to a subject in need thereof an effective amount of an agent which modulates a process in a pathway associated with epileptogenesis such that epileptogenesis is inhibited in the subject.
 2. A method for inhibiting epileptogenesis in a subject, comprising administering to a subject in need thereof an effective amount of an agent which antagonizes an NMDA receptor and augments endogenous GABA inhibition, such that epileptogenesis is inhibited in the subject.
 3. The method of claim 2, in which the agent antagonizes an NMDA receptor by binding to the glycine binding site of the NMDA receptors.
 4. The method of claim 2, in which the agent augments GABA inhibition by decreasing glial GABA uptake.
 5. The method of claim 2, in which the agent comprises a pharmacophore which both antagonizes an NMDA receptor and augments endogenous GABA inhibition.
 6. The method of claim 2, in which the agent is administered orally.
 7. The method of claim 6, in which, after the step of oral administration, the agent is transported into the nervous system of the subject by an active transport shuttle mechanism.
 8. The method of claim 2, in which the anti-epileptogenic agent is a β -amino anionic compound.
 9. The method of claim 8, in which an anionic moiety of the β -amino anionic compound is selected from the group consisting of carboxylate, sulfate, sulfonate, sulfinic acid, sulfamate, tetrazolyl, phosphate, phosphonate, phosphinate, and phosphorothioate.
 10. The method of claim 8, in which the agent is a β -amino acid.
 11. The method of claim 10, in which the agent is not β -alanine.
 12. The method of claim 2, further comprising administering the agent in a pharmaceutically acceptable vehicle.

13. A method for inhibiting epileptogenesis, comprising administering to a subject in need thereof an effective amount of a compound of the formula:



in which

A is an anionic group at physiological pH;

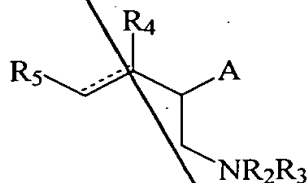
R₁ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aryloxy carbonyl, amino, hydroxy, cyano, halogen, carboxyl, alkoxy carbonyloxy, aryloxy carbonyloxy or aminocarbonyl; and

R₂ and R₃ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, or aryloxy carbonyl; or R₂ and R₃, taken together with the nitrogen to which they are attached, form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring;

or a pharmaceutically acceptable salt thereof;

such that epileptogenesis is inhibited.

14. A method for inhibiting epileptogenesis, comprising administering to a subject in need thereof an effective amount of a compound represented by the formula:



in which

the dashed line represents an optional single/double bond;

A is an anionic group at physiological pH;

R₂ and R₃ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, or aryloxy carbonyl; or R₂ and R₃, taken together with the nitrogen to which they are attached, form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring;

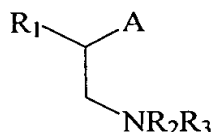
R₄ and R₅ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aryloxy carbonyl, amino, hydroxy,

cyano, alkoxy, aryloxy, carboxyl, alkoxycarbonyl, aryloxycarbonyl; or R₄ and R₅, taken together, form a substituted or unsubstituted carbocyclic or heterocyclic ring having from 5 to 15 atoms in the ring;

5 or a pharmaceutically acceptable salt thereof;
such that epileptogenesis is inhibited.

15. A method of inhibiting a convulsive disorder, comprising administering to a subject in need thereof an effective amount of a β -amino anionic compound such that the convulsive disorder is inhibited; with the proviso that the β -amino anionic compound is not β -alanine or taurine.

16. An anti-epileptogenic compound of the formula



15 in which

A is an anionic group at physiological pH;

R₁ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, amino, hydroxy, cyano, halogen, carboxyl, 20 alkoxycarbonyloxy, aryloxycarbonyloxy or aminocarbonyl; and

R₂ and R₃ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxycarbonyl; or R₂ and R₃, taken together with the nitrogen to which they are attached, form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring;

25 or a pharmaceutically acceptable salt thereof;
wherein the anti-epileptogenic compound has anti-epileptogenic activity.

17. The anti-epileptogenic compound of claim 16, in which A represents carboxylate.

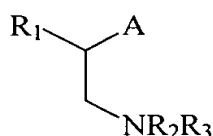
30 18. The anti-epileptogenic compound of claim 17, wherein said compound is selected from the group consisting of α -cyclohexyl- β -alanine, α -(4-tert-butylcyclohexyl)- β -alanine, α -(4-phenylcyclohexyl)- β -alanine, α -cyclododecyl- β -alanine, β -(*p*-methoxyphenethyl)- β -alanine, and β -(*p*-methylphenethyl)- β -alanine, and pharmaceutically-acceptable salts thereof.

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19. The anti-epileptogenic compound of claim 17, wherein said compound is selected from the group consisting of β -(4-trifluoromethylphenyl)- β -alanine and β -[2-(4-hydroxy-3-methoxyphenyl)ethyl]- β -alanine, and pharmaceutically-acceptable salts thereof.

5 20. The anti-epileptogenic compound of claim 17, wherein said compound is selected from the group consisting of β -(3-pentyl)- β -alanine and β -(4-methylcyclohexyl)- β -alanine, and pharmaceutically-acceptable salts thereof.

10 21. A pharmaceutical composition for treatment of epileptogenesis, comprising an anti-epileptogenic-effective amount of a compound of the formula



in which

15 A is an anionic group at physiological pH;

R₁ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aryloxy carbonyl, amino, hydroxy, cyano, halogen, carboxyl, alkoxy carbonyloxy, aryloxy carbonyloxy or aminocarbonyl; and

20 R₂ and R₃ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, or aryloxy carbonyl; or R₂ and R₃, taken together with the nitrogen to which they are attached, form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring;

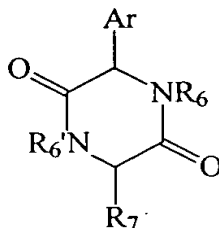
or a pharmaceutically acceptable salt thereof;

and a pharmaceutically-acceptable carrier.

25

22. A kit comprising a container of a compound of claim 16 and instructions for administering a therapeutically effective amount of the compound to a subject in need thereof such that epileptogenesis is inhibited in the subject.

30 23. A dioxapiperazine compound of the formula



in which

Ar represents an unsubstituted or substituted aryl group;

R₆ and R₆' are each independently hydrogen, alkyl, alkylcarbonyl, arylcarbonyl,
5 alkoxy carbonyl or aryloxy carbonyl; and

R₇ is hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl,
alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aryloxy carbonyl, cyano, carboxyl,
alkoxy carbonyl, aryloxy carbonyl, or -(CH₂)_n-Y, in which n is an integer from 1 to 4 and Y
is hydrogen or a heterocyclic moiety selected from the group consisting of thiazolyl,
10 triazolyl, and imidazolyl;

with the proviso that if Ar is an unsubstituted phenyl group, R₇ is not hydrogen,
methyl or phenyl;
or a pharmaceutically-acceptable salt thereof.

24. The dioxapiperazine compound of claim 23, wherein the carbon atom to which the
Ar group is attached has the D configuration

25. The dioxapiperazine compound of claim 23, wherein Ar is an unsubstituted or
substituted phenyl group.

26. The compound of claim 23, wherein Y is hydrogen.

27. The compound of claim 23, wherein R₇ is methyl or mercaptomethyl.

28. The compound of claim 23, wherein R₆ and R₆' are both hydrogen.

29. The compound of claim 23, wherein the compound is cyclophenylglycyl-2-(amino-
3-mercaptoputanoic acid).

30. The compound of claim 29, wherein the compound is cyclo-D-phenylglycyl-L-[2-
(amino-3-mercaptoputanoic acid)].

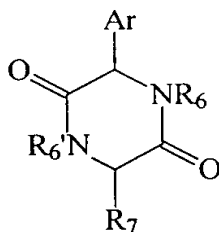
31. The compound of claim 25, wherein the compound is cyclo-D-phenylglycyl-(S-
Me)-L-cysteine.

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32. A pharmaceutical composition, comprising an anti-convulsant effective amount of a dioxapiperazine compound of claim 23.
- 5 33. A kit comprising a container of a compound of claim 23 and instructions for administering a therapeutically effective amount of the compound to a subject in need thereof such that a convulsive disorder is inhibited in the subject.
- 10 34. A method for inhibiting a convulsive disorder in a subject, comprising:
administering to a subject in need thereof an effective amount of an agent
which a) blocks sodium or calcium ion channels, or opens potassium or
chloride ion channels; and
b) has at least one activity selected from the group consisting of
NMDA receptor antagonism;
15 augmentation of endogenous GABA inhibition;
calcium binding;
iron binding;
zinc binding;
NO synthase inhibition; and
20 antioxidant activity;
such that epileptogenesis and ictogenesis is inhibited in the subject.
- 25 35. The method of claim 34, in which the agent antagonizes NMDA receptors by binding to the NMDA receptors.
36. The method of claim 35, in which the agent antagonizes NMDA receptors by binding to the glycine binding site of the NMDA receptors.
- 30 37. The method of claim 34, in which the agent augments GABA inhibition by decreasing glial GABA uptake.
38. The method of claim 34, in which the agent is administered orally.
- 35 39. The method of claim 34, further comprising administering the agent in a pharmaceutically acceptable vehicle.
40. The method of claim 34, in which the agent comprises a dioxapiperazine moiety.

41. The method of claim 34, in which the subject is a human.

42. A method for inhibiting a convulsive disorder, comprising administering to a
5 subject in need thereof an effective amount of a compound represented by the formula:



in which

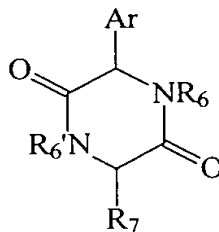
Ar represents an unsubstituted or substituted aryl group;
10 R₆ and R₆' are each independently hydrogen, alkyl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl or aryloxy carbonyl; and

R₇ is hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aryloxy carbonyl, cyano, carboxyl, alkoxy carbonyl, aryloxy carbonyl, or -(CH₂)_n-Y, in which n is an integer from 1 to 4 and Y
15 is hydrogen or a heterocyclic moiety selected from the group consisting of thiazolyl, triazolyl, and imidazolyl;

with the proviso that if Ar is unsubstituted phenyl, R₇ is not hydrogen, methyl or unsubstituted phenyl;

or a pharmaceutically acceptable salt thereof;
20 such that the convulsive disorder is inhibited.

43. A compound of the formula



in which

5 Ar represents an unsubstituted or substituted aryl group;

R₆ is hydrogen or alkyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or aryloxy carbonyl;

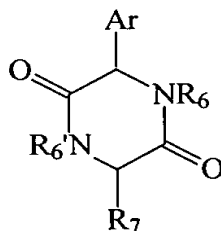
10 R₆' is selected from the group consisting of an antioxidant moiety, an NMDA antagonist, an NO synthase inhibitor, an iron chelator moiety, a Ca(II) chelator moiety, and a Zn(II) chelator moiety; and

15 R₇ is hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxy carbonyl, cyano, carboxyl, alkoxycarbonyl, aryloxy carbonyl, or -(CH₂)_n-Y, in which n is an integer from 1 to 4 and Y is a heterocyclic moiety selected from the group consisting of thiazolyl, triazolyl, and imidazolyl; or a pharmaceutically-acceptable salt thereof.

44. The compound of claim 43, wherein R₆' is D-α-aminoadipyl.

20 45. The compound of claim 44, wherein R₇ is mercaptomethyl.

46. A pharmaceutical composition comprising a compound of the formula

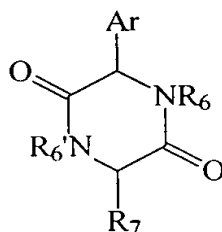


25 in which

Ar represents an unsubstituted or substituted aryl group;

R₆ is hydrogen or alkyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or aryloxy carbonyl;

49. A method for treating a disorder associated with NMDA receptor antagonism, comprising administering to a subject in need thereof an effective amount of a compound of the formula:



5 in which

Ar represents an unsubstituted or substituted aryl group;

R₆ is hydrogen or alkyl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl or aryloxy carbonyl;

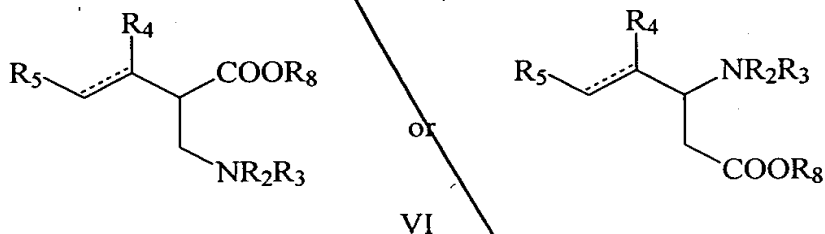
R₆' is an NMDA antagonist moiety;

10 R₇ is hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aryloxy carbonyl, cyano, carboxyl, alkoxy carbonyl, aryloxy carbonyl, or -(CH₂)_n-Y, in which n is an integer from 1 to 4 and Y is a heterocyclic moiety selected from the group consisting of thiazolyl, triazolyl, and imidazolyl;

15 or a pharmaceutically-acceptable salt thereof; and

such that the disorder associated with NMDA receptor antagonism is treated.

50. A method for preparing a β-amino carboxyl compound represented by formula VI:



20

in which

the dashed line represents an optional single/double bond;

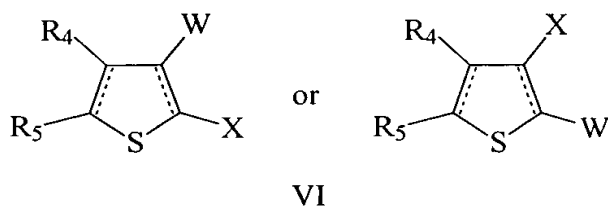
25 R₂ and R₃ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, or aryloxy carbonyl; or R₂ and R₃, taken together with the nitrogen to which they are attached, form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring;

R₄ and R₅ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aryloxy carbonyl, amino, hydroxy, cyano, carboxyl, alkoxy carbonyl, or aryloxy carbonyl; or R₄ and R₅, taken together form a

substituted or unsubstituted carbocyclic or heterocyclic ring having from 5 to 15 atoms in the ring, and

R_8 is hydrogen, alkyl, aryl, or an organic or inorganic salt-forming cation;
the method comprising:

5 reacting a compound of formula VII



in which

the dashed lines each represent an optional single bond;

10 X is nitro, azido, or NR_2R_3 , wherein R_2 and R_3 are defined above;

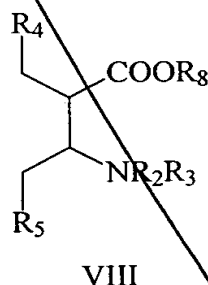
W is $-CN$ or $-COOR_8$;

R_4 and R_5 are as defined above; and

R_8 is hydrogen, alkyl, aryl, or an organic or inorganic salt-forming cation;

15 under reductive desulfurization conditions such that the β -amino carboxyl compound is formed.

51. A method for preparing a β -amino carboxyl compound represented by formula VIII:

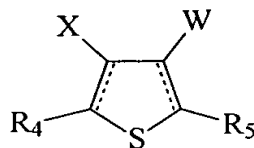


20 in which

R_2 and R_3 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, or aryloxy carbonyl; or R_2 and R_3 , taken together with the nitrogen to which they are attached, form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring;

25 R_4 and R_5 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aryloxy carbonyl, amino, hydroxy, cyano, alkoxy, aryloxy, carboxyl, alkoxy carbonyl, aryloxy carbonyl; or R_4 and R_5 , taken together, form a substituted or unsubstituted carbocyclic or heterocyclic ring having from 5 to 15 atoms in the ring; and

30 R_8 is hydrogen, alkyl, aryl, or an organic or inorganic salt-forming cation;
the method comprising reacting a compound of formula IX



IX

in which

the dashed lines each represent an optional single/double bond;

X is nitro, azido, or NR_2R_3 , wherein R_2 and R_3 are defined above;

W is $-\text{CN}$ or $-\text{COOR}_8$;

R_8 is hydrogen, alkyl, aryl, or an organic or inorganic salt-forming cation; and

R_4 and R_5 are as defined above; under reductive desulfurization conditions such that the β -amino carboxyl compound of Formula VIII is formed;

with the proviso that if W is $-\text{CN}$, the method comprises the further step of acidification.

52. The method of claim 50, wherein R_2 is alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, or aryloxy carbonyl, and R_3 is hydrogen.

53. A method for inhibiting epileptogenesis and ictogenesis in a subject, comprising administering to a subject in need thereof an effective amount of an agent represented by the formula A-B, in which

A is a domain having sodium or calcium ion channel blocking activity, or A has potassium or chloride channel opening activity; and

B is a domain having at least one activity selected from the group consisting of

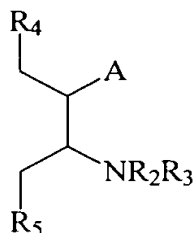
- NMDA receptor antagonism;
- augmentation of endogenous GABA inhibition;
- calcium binding;
- iron binding;
- zinc binding;
- NO synthase inhibition; and
- antioxidant activity;

such that epileptogenesis is inhibited in the subject.

54. The method of claim 53, in which the domains A and B of the agent are covalently linked.

55. The method of claim 53, in which A is a dioxapiperazine moiety.

56. A method for inhibiting epileptogenesis, comprising the step of administering to a subject in need thereof an effective amount of a compound represented by the formula:



in which

5 A is an anionic group at physiological pH;

R₂ and R₃ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, or aryloxy carbonyl; or R₂ and R₃, taken together with the nitrogen to which they are attached, form an unsubstituted or substituted heterocycle having from 3 to 7 atoms in the heterocyclic ring;

10 R₄ and R₅ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aryloxy carbonyl, amino, hydroxy, cyano, alkoxy, aryloxy, carboxyl, alkoxy carbonyl, or aryloxy carbonyl; or R₄ and R₅, taken together, form a substituted or unsubstituted carbocyclic or heterocyclic ring having from 5 to 15 atoms in the ring;

15 or a pharmaceutically acceptable salt thereof;
such that epileptogenesis is inhibited.

57. The method of claim 56, in which A represents a carboxylate.

20 58. A method for inhibiting a neurological condition in a subject, the method comprising administering to a subject in need thereof an effective amount of an agent which antagonizes an NMDA receptor and augments endogenous GABA inhibition, such that the neurological condition is inhibited in the subject, wherein the neurological condition is selected from the group consisting of stroke, Alzheimer's disease, cancer, and
25 neurodegenerative disease.

59. A method for preparing a β -aryl- β -alanine compound, comprising:
reacting an aryl aldehyde with a malonate compound and an ammonium compound,
under conditions such that a β -aryl- β -alanine compound is formed.

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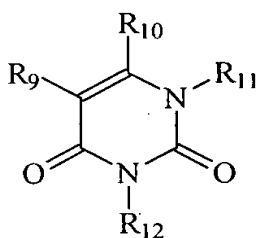
60. The method of claim 59, wherein the aryl aldehyde is a substituted or unsubstituted benzaldehyde.

61. The method of claim 59, wherein the malonate compound is malonic acid.

62. The method of claim 59, wherein the ammonium compound is an ammonium salt of a compound selected from the group consisting of ammonia, primary amines, and secondary amines.

63. The method of claim 59, wherein the solvent is a polar organic solvent.

64. A method for inhibiting epileptogenesis, the method comprising the step of administering to a subject in need thereof an effective amount of a compound represented by the formula:



in which

R₉ and R₁₀ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, amino, hydroxy, thiol, alkylthiol, nitro, cyano, halogen, carboxyl, alkoxycarbonyloxy, aryloxycarbonyloxy and aminocarbonyl; or R₉ and R₁₀, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring; and

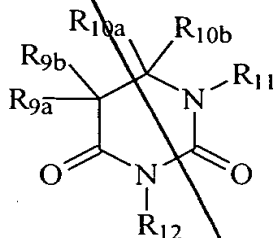
R₁₁ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxycarbonyl; or R₁₀ and R₁₁, together with the carbon atom and nitrogen atom to which they are respectively attached, are joined to form a heterocyclic ring having from 4 to 8 members in the ring; and R₁₂ is selected from the group consisting of hydrogen, alkyl, aryl and a carbohydrate;

or a pharmaceutically acceptable salt thereof;

such that epileptogenesis is inhibited.

65. The method of claim 64, in which R₁₁ is hydrogen.

66. A method for inhibiting epileptogenesis, comprising the step of administering to a subject in need thereof an effective amount of a compound represented by the formula:



5 in which

R_{9a}, R_{9b}, R_{10a}, R_{10b} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxy carbonyl, amino, hydroxy, thiol, alkylthiol, nitro, cyano, halogen, carboxyl, alkoxycarbonyloxy, aryloxy carbonyloxy and aminocarbonyl; or

10 R_{9a} and R_{9b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring; or R_{10a} and R_{10b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring; or

15 one of R_{9a} and R_{9b} is joined with one of R_{10a} and R_{10b}, together with the two-carbon unit to which they are attached, to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;

20 R₁₁ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxy carbonyl; or one of R_{10a} and R_{10b} is joined with R₁₁, together with the carbon atom and nitrogen atom to which they are respectively attached, to form a heterocyclic ring having from 4 to 8 members in the ring; and

25 R₁₂ is selected from the group consisting of hydrogen, alkyl, aryl and a carbohydrate (such as a sugar, e.g., ribose or deoxyribose);
or a pharmaceutically acceptable salt thereof;
such that epileptogenesis is inhibited.

67. The method of claim 65, in which R₁₁ is hydrogen.

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